Br. J. clin. Pharmac. (1983), **16**, 365S–369S

BROTIZOLAM: STUDIES OF EFFECTS ON SLEEP AND ON PERFORMANCE IN YOUNG ADULTHOOD AND IN MIDDLE AGE

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1 Effects of brotizolam (0.2, 0.4 and 0.6 mg), on sleep and performance, were studied in young adults. All doses increased total sleep time, improved the sleep efficiency index, and reduced drowsy sleep and number of awakenings. Brotizolam (0.4 and 0.6 mg) also reduced awake activity. There was some evidence of a delay to the first REM period, but only 0.6 mg reduced the total duration of REM sleep. There were no changes in slow wave sleep. Visuomotor coordination was impaired up to 15.0 h after overnight ingestion of 0.6 mg, but there were no residual effects after the overnight ingestion of 0.2 mg, and with 0.4 mg residual effects did not persist beyond 9.5 h.

2 In middle-aged subjects 0.25 and 0.5 mg were studied. The lower dose (0.25 mg) increased total sleep time, and improved the sleep efficiency index, shortened sleep onset latency, and reduced drowsy sleep. The effect of the higher dose (0.5 mg) was more marked. In a performance study using digit symbol substitution, no residual effect was observed after 0.25 mg brotizolam.

3 Brotizolam is a short-acting hypnotic. Doses up to 0.25 mg are likely to prove adequate over the main span of life and be free of adverse effects on sleep and residual effects on performance.

Keywords brotizolam sleep performance young adults middle-aged subjects

Introduction

Over the past few years several benzodiazepines have been developed with the aim of providing hypnotics which lack residual effects on performance. In particular, heterocyclic ring structures have been introduced across the 1,2-position, and one of the resultant compounds, brotizolam, is a potent drug with the advantage of low toxicity. Studies in man have shown that it is rapidly excreted, so it may be particularly useful in the management of insomnia when residual sequelae must be avoided. We have studied effects on sleep and on performance in young adulthood and in middle age, and these studies are reviewed in this paper.

Methods

Studies on sleep

The studies in young adults were carried out with 0.2, 0.4 and 0.6 mg doses of brotizolam on six healthy males (Nicholson *et al.*, 1980). They were aged between 18 and 27 (mean 22) years. In the studies on the sleep of middle age the subjects were six healthy males aged between 46 and 51 (mean 48) years (Nicholson *et al.*, 1982), and 0.25 and 0.5 mg doses were used.

Subjects were required to refrain from napping and undue exercise and to abstain from alcohol for 24 h and from caffeine for at least 12 h before the recordings. Subjects reported 1.5 h before bedtime. The individual bedrooms were light-proofed, sound-attenuated and temperature (18 ± 1 °C) and humidity (55 ± 1%) controlled. In an adjoining room three channels of electroencephalographic activity were recorded (C4-A1, P1-T5 and OzPz-O3), together with the electromyogram and electro-oculograms.

Each sleep record was scored independently into 30 s epochs by two analysts according to the criteria of Rechtschaffen & Kales (1968). Differences in the annotation of sleep stages between the scores were resolved, but did not occur in more than 5 per cent of the epochs. These data and subjective assessments were analysed statistically. The coefficient of variability (s.d. × 100/mean) of each measure (C/V) was examined to decide whether an

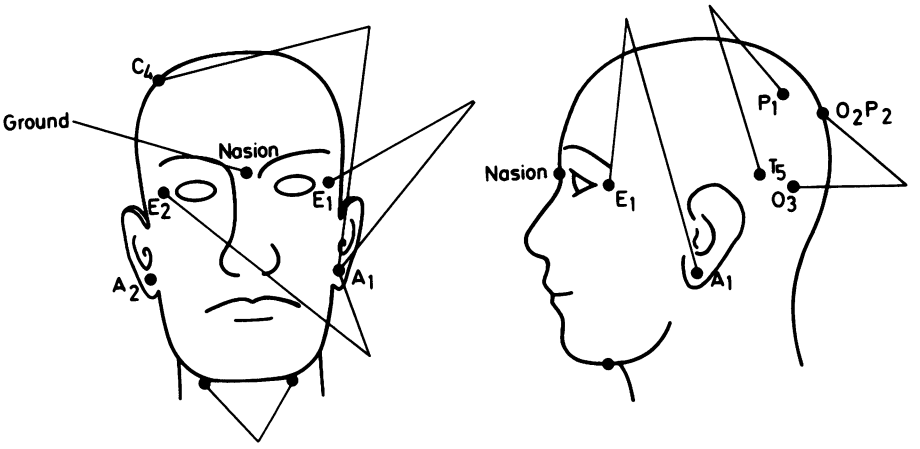

Figure 1 Details of recording technique.

analysis of variance was appropriate. If the value exceeded 50 per cent a nonparametric method was used (Friedman two-way analysis of variance).

Two adaptation nights with ingestion of placebo, separated by 1 week, preceded each study. All medication was identical in appearance and the experimental stage of each study was double-blind. Treatments were presented in random order and 1 week separated each assessment from the next. Subjective assessment of sleep and well-being were measured using visual analogue scales. Thirty minutes after awakening, each subject completed four assessments. The assessments and extremes of the 100 mm analogue scales were—A: I slept, very poorly—very well; B: Now I feel, very sleepy—wide awake; C: I fell asleep, never—immediately and D: After I fell asleep I slept, very badly—very well. In each case a favourable response tended toward the 100 extreme of the scale.

Performance studies

Performance studies were carried out with 0.2, 0.4 and 0.6 mg doses of brotizolam in six healthy females aged between 19 and 32 (mean 24) years (Nicholson *et al.*, 1980), and with 0.25 mg only in six healthy males aged between 45 and 54 (mean 48) years (Nicholson & Stone, unpublished data). They were required to avoid napping and undue exercise, and similar restrictions to those outlined previously regarding the use of alcohol and caffeine were adopted.

The young adults were trained on a visuo-motor coordination task (Borland & Nicholson, 1974) until they had reached steady performance. They were required to position a spot inside a randomly moving circle displayed on an oscilloscope, using a hand-held stick, and an error signal proportional to the distance between the spot and the centre of the circle controlled the difficulty of the task by modulating the mean amplitude of the movement of the circle. The position of the circle and spot, and so the radial error, were recorded. Each experimental run lasted 10 min. The subjects reached a plateau performance within 100 s, after which scoring began. The laboratory was sound-attenuated and air-conditioned.

Overnight ingestion of 0.2, 0.4 and 0.6 mg brotizolam and morning ingestion of 0.4 mg allowed the measurement of immediate and residual effects on performance. Subjects took matched drugs and/or placebos at 'lights out' (23.00 h) and at 08.00 h, and were therefore unaware whether the immediate or residual consequences were being studied. Performance was measured at 08.30, 09.30, 11.30, 13.30 and 16.00 h, and so immediate effects were recorded at 0.5, 1.5, 3.5, 5.5 and 8 h and residual sequelae at 9.5, 10.5, 12.5, 14.5 and 17 h after ingestion. The trial was double-blind with treatments arranged in random order each separated by 1 week from the next. Comparisons between post-drug and post-placebo measures were made using analysis of variance.

The performance studies in middle age were carried out as part of an investigation on the activity of an imidazodiazepine (Nicholson & Stone, unpublished data). In this study brotizolam was used an active control in a single dose of 0.25 mg. Performance was measured 9 h after the overnight ingestion of the drug. The test used was coding ability as measured by the digit symbol substitution test. A series of 100 different sheets each with 200 randomised digits (0–9) arranged in 10 rows were presented to each subject. In the

space under each digit the subjects were required to write the appropriate symbol indicated by a code at the top of each page. The code was different for each of the 100 sheets. In each session subjects were given two sheets and 2 min timed separately to complete as many substitutions as possible for each sheet. In all tests and for all subjects errors were rare and only the number attempted was analysed.

Results

Sleep in young adults (0.2, 0.4 and 0.6 mg brotizolam)

Brotizolam increased total sleep time, reduced drowsy sleep and improved the sleep efficiency index, and the 0.4 and 0.6 mg doses also reduced awake activity. There were no changes in slow wave sleep. An effect of individual doses on latency to rapid eye movement (REM) sleep was not established, but by pooling results the latency was increased over the dose range. However, the effect was not consistent. The mean duration and percentage of REM sleep were reduced at all three doses during the first 6 h of sleep, particularly in the first 2 h interval, but over the whole night REM sleep and the REM/NREM ratio were reduced with the highest dose (0.6 mg) only. The subjects as a group assessed that their sleep was improved over the whole dose range; they fell asleep more quickly and, after they had fallen asleep, they slept better. Assessments of well being the next morning suggested that a residual effect may have been detected after 0.6 mg only, but this did not reach significance ($P < 0.05$).

Sleep in the middle aged (0.25 and 0.5 mg brotizolam)

The lower dose of brotizolam increased total sleep time and improved the sleep efficiency index, shortened the sleep onset latency, reduced drowsy sleep and increased stage 2 sleep. The higher dose (0.5 mg) also increased total sleep time and the sleep efficiency index, as well as reducing drowsy sleep and increasing stage 2. The subjects assessed their sleep as improved and the subjective assessments related to residual effects were not significantly altered for the subjects as a group.

Performance in young adults (0.2, 0.4 and 0.6 mg brotizolam)

After morning ingestion of 0.4 mg, impaired performance was observed from 0.5 to 5.5 h. There were no residual effects with 0.2 mg brotizolam,

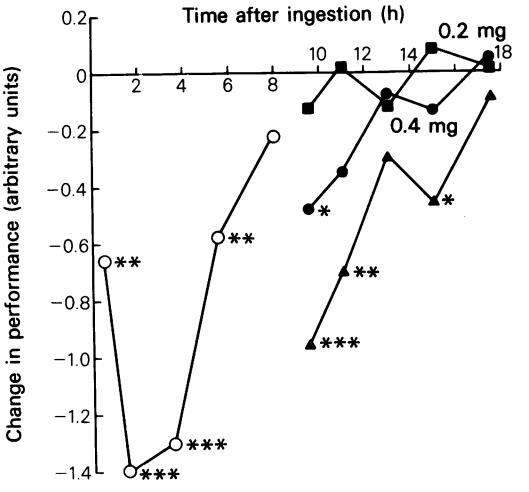

Figure 2 Immediate and residual effects of brotizolam on visuo-motor coordination (arbitrary units). Open symbols-morning ingestion. Filled symbols-overnight ingestion. ■ 0.2 mg; ○, ● 0.4 mg; △ 0.6 mg. Significance levels $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

but there was a residual effect with 0.4 mg at 9.5 h and with 0.6 mg at 9.5, 10.5 and 15 h. After ingestion impaired performance over the dose range 0.2–0.6 mg showed a linear effect at 10.5 h. The subjects did not assess their performance as impaired, although as a group they considered that their ability to concentrate after the morning ingestion of 0.4 mg had deteriorated.

Performance in middle age (0.25 mg brotizolam only)

There was no effect of 0.25 mg brotizolam on the digit symbol substitution test 9 h after overnight ingestion, though changes were observed with the imidazo-benzodiazepine being investigated in the study.

Discussion

The effect of brotizolam on performance has been studied previously by Grünberger *et al.* (1978). Normal subjects received 0.1, 0.3 and 0.5 mg brotizolam, and measurements of performance were made 2, 4, 6 and 8 h after ingestion. Effects were dose-dependent. Brotizolam 0.1 and 0.3 mg impaired attention for at least 2 h after ingestion, while 0.5 mg impaired attention and decreased motor activity for at least 6 h and reduced concentration for at least 8 h. These

observations are comparable with the present data, though we also observed performance after overnight ingestion and with 0.4 mg found it to be impaired for about 10 h, so a time-of-day effect may exist. Performance may recover more quickly on a task being practised throughout the period of a drug effect, or impairment may be greater in the early morning because of a synergistic effect with the relatively low level of performance. Rates of metabolism may also differ with time of day, so the residual effects of a drug to be taken at night may not be accurately defined by daytime studies.

In the young adults, over the dose range 0.2–0.6 mg, there was a marked improvement in the sleep efficiency index, so there is broad agreement with Saletu *et al.* (1979), who, using the spectral density of the electroencephalogram, predicted hypnotic activity over the dose range 0.3–0.5 mg. In our studies 0.4 mg brotizolam increased total sleep time and reduced awake activity and drowsy sleep without adverse changes in REM and slow wave sleep, but the effect of 0.2 mg was equally useful. It increased total sleep time, and reduced drowsy sleep and number of awakenings. These studies on sleep and the performance data suggest that a dose around 0.25 mg would be appropriate and would also be free of residual sequelae.

The sleep of middle age is more disturbed than that of the young adult. Total sleep time tends to be shorter, and the sleep period contains more awake and drowsy activity, so it may be expected that hypnotics would easily improve the sleep of this age group. Nevertheless, we have observed that diazepam and temazepam are less effective in middle age than would be predicted from studies with the same drugs in young adults (Nicholson & Stone, 1979) and it is in the context of the variable effect of hypnotics across the span of life that we returned to this problem with brotizolam. It would appear that 0.25 mg brotizolam is as effective in middle age as in young adulthood and the study on performance in the former age group shows that it is also free of residual sequelae.

Brotizolam is a short-acting hypnotic and it is likely to be useful as an initial approach to the management of sleep difficulties. However, it is a potent drug and careful attention must be given to dose. A dose range up to 0.25 mg is likely to prove adequate over the main span of life and to be free of adverse effects on sleep and residual effects on performance.

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Brotizolam: Schlaf- und Leistungsuntersuchungen bei jungen Erwachsenen und Personen mittleren Alters

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1 Die Wirkungen von Brotizolam (0,2, 0,4, und 0,6 mg) auf Schlaf und Leistungsfähigkeit wurde bei jungen Erwachsen untersucht. Sämtliche Dosierungen erhöhten die Gesamtschlafzeit, verbesserten den Schlafeffizienzindex und reduzierten den oberflächlichen Schlaf sowie die Aufwachhäufigkeit. 0,4 und 0,6 mg reduzierten ebenfalls die Wachaktivität im Schlaf. Es gab Hinweise auf eine Verzögerung der ersten REM-Phase, jedoch nur 0,6 mg reduzierten die Gesamtdauer des REM-Schlafs. Veränderungen des Deltawellen Schlafs traten nicht auf. Die visuomotorische Koordination war bis zu 15 Stunden nach der abendlichen Einnahme von 0,6 mg beeinträchtigt, aber es gab

keine Nachwirkungen nach der abendlichen Einnahme von 0,2 mg; bei 0,4 mg hielten die Nachwirkungen nicht länger als 9.5 Stunden an.

2 Bei Versuchspersonen mittleren Alters wurden Dosen von 0,25 und 0,5 mg untersucht. Die niedrigere Dosierung (0,25 mg) verlängerte den Gesamtschlaf und verbesserte den Schlafeffizienzindex, verkürzte die Einschlafzeit und reduzierte den oberflächlichen Schlaf. Die Wirkung der höheren Dosierung (0,5 mg) war stärker ausgeprägt. In einem Leistungstest mit Ziffer-Symbol-Austausch wurden keine Nachwirkungen nach 0,25 mg Brotizolam beobachtet.

3 Brotizolam ist ein kurz wirkendes Schlafmittel. Dosen bis zu 0,25 mg dürften für den größten Teil des Lebens ausreichend sein; sie haben keine unerwünschten Effekte auf den Schlaf und auch keine Nachwirkungen auf die Leistungsfähigkeit.

Brotizolam: Etudes du sommeil et de ses performances chez des adultes jeunes et d'âge mûr

A.N. NICHOLSON

1 Les effets du brotizolam (0,2, 0,4 et 0,6 mg) sur le sommeil et les performances ont été étudiés chez de jeunes adultes. Toutes les doses ont augmenté la durée totale du sommeil, amélioré l'indice d'éfficacité de celui-ci et réduit le demi-sommeil et le nombre d'éveils. Les doses de 0,4 et 0,6 mg ont également réduit l'activité de veille. Il y a eu quelques indications d'un retardement de la première phase MOR, mais seule la dose de 0,6 mg a réduit la durée totale du sommeil MOR. Il n'ya pas eu de modification du sommeil à ondes lentes. La coordination visuomotrice a été affectée jusqu'à 15,0 h après l'ingestion nocturne de 0,6 mg, mais aucun effet résiduel n'a été observé après l'ingestion nocturne de 0,2 mg, et les effets suscités par la dose de 0,4 mg n'ont pas persisté au-delà de 9,5 h.

2 L'effet de 0,25 et 0,5 mg de brotizolam a été étudié chez des sujets d'âge mûr. La dose inférieure (0,25 mg) a augmenté la durée totale du sommeil, amélioré l'indice d'éfficacité du sommeil, abrégé le temps de latence jusqu'au début du sommeil et réduit le demi-sommeil. L'effet de la dose supérieure (0,5 mg) a été plus prononcé. Une étude des performances utilisant la substitution de chiffres par des symboles n'a pas mis en évidence d'effet résiduel après la prise de 0,25 mg de brotizolam.

3 Le brotizolam est un hypnotique d'action brève. Des doses jusqu'à 0,25 mg conviennent probablement pour la plus grande partie de la vie sans exercer d'action négative sur le sommeil ni avoir d'effets résiduels sur les performances.

Brotizolam: Estudios del sueño y del rendimiento en adultos jóvenes y de mediana edad

A.N. NICHOLSON

1 En adultos jóvenes se estudiaron los efectos de brotizolam (0,2, 0,4 y 0,6 mg) sobre el sueño y el rendimiento. Todas las dosis aumentaron el tiempo de sueño total, mejoraron el índice de eficiencia del sueño y redujeron el sueño amodorrado y el número de despertares. 0,4 y 0,6 mg también redujeron la actividad de vigilia. Hubo algún indicio de retardo en la presentación del primer período REM, pero solamente 0,6 mg redujeron la duración total del sueño REM. No se produjeron alteraciones en el sueño de onda lenta. La coordinación visual-motora se vió afectada hasta 15,0 horas después de la ingestión nocturna de 0,6 mg, pero no hubo efectos residuales después de la ingestión nocturna de 0,2 mg, mientras que con 0,4 mg los efectos residuales no persistieron más allá de 9,5 horas.

2 En individuos de mediana edad se estudiaron 0,25 y 0,50 mg. La dosis inferior (0,25 mg) aumentó el tiempo de sueño total y mejoró el índice de eficiencia del sueño, acortó el período de latencia de comienzo del sueño y redujo el sueño amodorrado. El efecto de la dosis superior (0,5 mg) fue más marcado. En un estudio del rendimiento utilizando la prueba de sustitución de dígitos por símbolos no se observaron efectos residuales de ningún tipo después de 0,25 mg de brotizolam.

3 Brotizolam es un hipnótico de acción breve. Es probable que dosis de hasta 0,25 mg demuestren ser adecuadas para la mayor parte de la vida y sin efectos desfavorables sobre el sueño ni efectos residuales sobre el rendimiento.